Chapter 1
Background

Basement membranes are thin layers of extracellular connective tissue that divide epithelial cells from the underlying connective tissue or from different types of cells [1]. Basement membranes are very complex structures that play different roles and have different compositions and structures, depending on the type of tissue they are found in. Functionally, basement membranes play many different roles. For instance, they are the site of attachment for many cells; can influence the behavior of cells such as their growth, apoptosis, development, and differentiation; and can also be the backbone structure for cell and tissue repair. The basement membrane can also regulate the extracellular environment of cells by acting as a selectively permeable structure. In this book, we will specifically be discussing the structure of the epidermal basement membrane, because many of the diseases that we will discuss will require a basic understanding of this important type of basement membrane.

The epidermal basement membrane consists of four major layers [2]. The first layer is called the basal keratinocyte layer, and it consists of the plasma membrane of the basal layer of keratinocytes, the hemidesmosomes, and cytoskeletal keratin intermediate filaments inside the keratinocyte, which connect to the hemidesmosomes. The second layer is called the lamina lucida, and it contains the extracellular connections, also known as anchoring filaments, that run between the hemidesmosomes and the lamina densa [3]. The lamina densa, also known as the basement membrane proper, is the next layer of the basement membrane found beneath the lamina lucida. The fourth layer of the basement membrane is the sublamina densa region, which consists of anchoring fibrils, microfibrils, interstitial collagens, micro-thread-like fibers, and anchoring plaques, which are components of the papillary dermis that connect it to the lamina densa above (Fig. 1.1).

Acquired immune vesiculobullous diseases are diseases in which the body starts to produce autoantibodies against protein antigens in the epidermis or in the basement membrane associated with the epidermal cells [4]. Acquired immunobullous diseases can be divided into epidermal pemphigus or subepidermal pemphigoid diseases. Pemphigus diseases involve autoantibodies against proteins in the epidermis,

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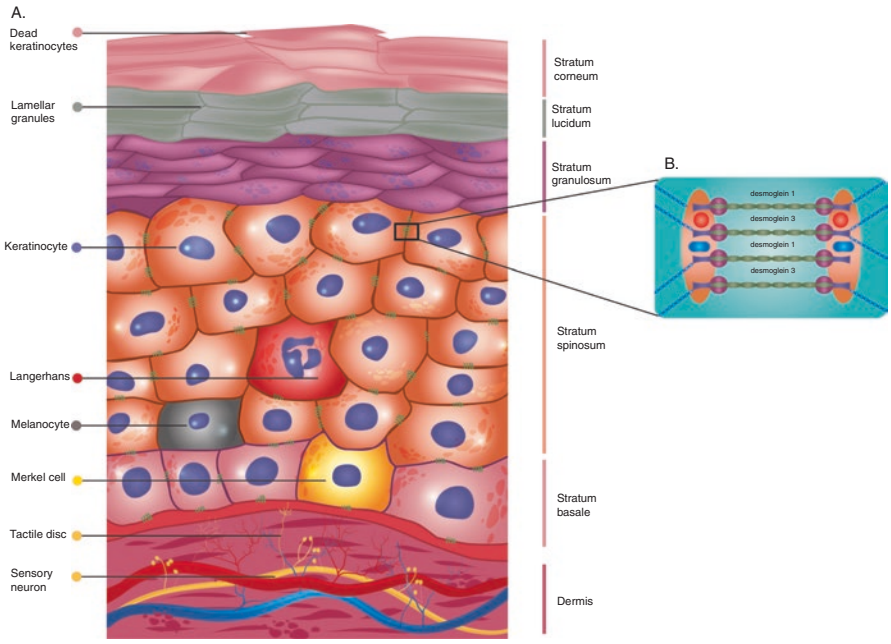

Fig. 1.1 Anatomy of the basement membrane. (**a**) The five layers of epidermis, which include the superficial layer of stratum corneum, stratum lucidum, stratum granulosum, stratum spinosum, and the innermost layer of stratum basale. Stratum corneum is made up of dead keratinocytes that are linked together with proteins. Stratum lucidum contains dead keratinocytes that have not completely finished the keratinization process. Stratum granulosum is the layer containing keratinocytes that contain keratohyalin granules. Stratum spinosum is characterized by the presence of desmosomes that results in an impermeable junction between keratinocytes as seen in section B of this image. Stratum basale is the deepest layer of epidermis, which contains a single layered column of epidermal stem cells. Moreover, the epidermis also contains specialized cells that are most prominent in stratum spinosum. For example, Langerhans are present in all stratums except stratum corneum, and their primary function is to fight skin infections by becoming antigen-presenting cells. Melanocytes are melanin-producing cells responsible for skin color. Merkel cells contain mechanoreceptors responsible for the detection of light touches. (**b**) The desmosome junction between keratinocytes that is created by the binding of desmoglein 1 (dsg1) and desmoglein 3 (dsg3) antibodies that attach to cell surface (Source: Pooya Khan Mohammad Beigi)

whereas the pemphigoid group of diseases involves subepidermal autoantibodies against proteins in the basement membrane associated with the epidermis.

Pemphigus

The pemphigus group of diseases are immune diseases involving immunoglobulin G (IgG) autoantibodies against various proteins found on the surface of epidermal cells [1]. This group of diseases is divided into three main disease groups:

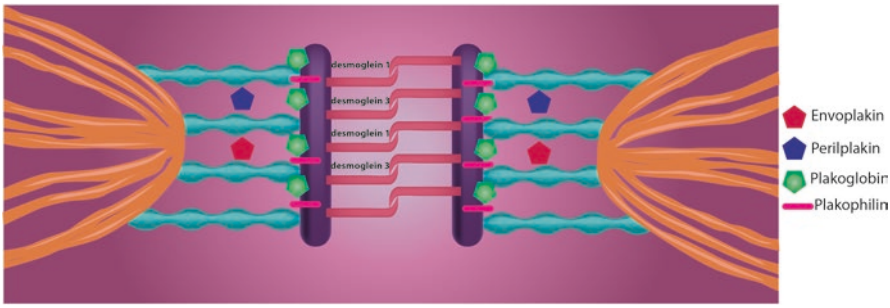

Fig. 1.2 The junction between keratinocytes that is characterized by desmosomes, which create an impermeable junction between the cells. The desmosome junction is created by the binding of desmoglein 1 (dsg1) and desmoglein 3 (dsg3) antibodies that attach to cell surface. As seen in the image, the junction is created with the help of additional proteins. For example, envoplakins interact with periplakins in order to serve as an intermediate filament in the desmosome junction. The plakoglobin serves as the cytoplasmic component. Lastly, plakophilins are proteins that link cadherins to intermediate filaments in the junction (Source: Pooya Khan Mohammad Beigi MD)

pemphigus vulgaris, pemphigus foliaceus, and paraneoplastic pemphigus. Pemphigus foliaceus involves autoantibodies against desmoglein 1 proteins, and paraneoplastic pemphigus involves autoantibodies against both desmoglein and plakin. There are two different variants of pemphigus vulgaris: one is the mucocutaneous variant and the other is the mucosal dominant variant [1]. The mucosal dominant variant of pemphigus vulgaris involves autoantibodies against only desmoglein 3, whereas the mucocutaneous variant involves autoantibodies against both desmoglein 1 and 3 (Fig. 1.2).

Desmoglein Compensation Hypothesis of Pemphigus Disease Presentation

On mucosal surfaces, both desmoglein 1 and 3 are expressed; however, desmoglein 3 dominates in terms of its expression in the mucosa compared to desmoglein 1 [5]. In the skin epidermis, desmoglein 1 is expressed everywhere, but is mainly expressed in the superficial upper layers of the skin epidermis, whereas desmoglein 3 is expressed in the basal lower layers of the epidermis. These differences have been hypothesized to explain the clinical features of various presentations of pemphigus based on the autoantibodies involved [6]. For instance, pemphigus vulgaris involves autoantibodies primarily directed against desmoglein 3 proteins, and since these proteins are rendered dysfunctional by the antibodies, the keratinocytes in the lower basal layers of the epidermis become detached from one another, resulting in the blisters in the basal layers of the epidermis [5]. In pemphigus foliaceus, the skin blisters are more superficial, and this can be explained by the fact that this disease involves autoantibodies to desmoglein 1, which is mainly expressed in the

superficial layers of the epidermis. Pemphigus foliaceus has no mucosal erosions simply because desmoglein 3 dominates in terms of its expression in the mucous membranes [5].

Pemphigus vulgaris has two primary clinical variants, and the clinical features of these two variants can also be explained based on desmoglein expression. The mucocutaneous variant that involves autoantibodies against desmoglein 1 and 3 causes mucosal erosions and deep skin blisters [5]. The mucosal dominant variant that involves antibodies against desmoglein 3 only causes mucosal erosions and no skin lesions, because the desmoglein 1 in the lower epidermal layers makes up for the lack of desmoglein 3; however, in the mucous membranes, there is not enough desmoglein 1 to make up for the lack of desmoglein 3, since desmoglein 3 is expressed in greater quantity than desmoglein 1 in the mucous membranes [5]. There is a minority of patients that have cutaneous-only disease expression (i.e., no current or history of mucosal lesions) that cannot be fully explained by the desmoglein 3/1 compensation hypothesis. Recent literature indicates that pemphigus vulgaris patients harbor antibodies to other, nondesmoglein, targets [7–9].

Types of Pemphigus Diseases

Pemphigus Vulgaris (Explained in Detail in the Next Section)

Pemphigus Vegetans

Pemphigus vegetans is a clinical variant of pemphigus vulgaris that involves erosions that form fungoid or papillomatous growths. These fungoid or vegetative growths are mainly seen on the scalp or face. This clinical variant is fairly rare and involves two subtypes: mild Hallopeau and severe Neumann types [1].

Pemphigus Foliaceus

Pemphigus foliaceus only has cutaneous erosions and does not involve any mucosal erosions. It is an autoimmune disease in which the body produces IgG autoantibodies against desmoglein 1 proteins on the surface of keratinocytes in the superficial upper layers of the epidermis. The erosions look crusted and scaly in appearance and are transient in nature. These erosions also have an erythematous base. These erosions are found mainly on the upper trunk, scalp, and face [10].

Pemphigus foliaceus is similar to pemphigus vulgaris with respect to the fragile blisters that are rarely ever found intact; thus, we only see the crust and scaly erosions left over from the ruptured superficial vesicles [10]. In this disease, the Nikolsky sign is present. The Nikolsky sign involves pushing the top of a blister and observing whether the top epidermal layers of the blister move laterally. This would indicate the absence of intercellular connections holding the top layers of epidermal cells together. Patients that have this disease often complain of painful burning lesions.

Pemphigus Erythematosus

This is also known as the Senear-Usher syndrome [1]. This is considered to be a type of pemphigus foliaceus that is only found on the malar region of the face. So it is a variant of pemphigus foliaceus, in which the crusted lesions only appear on the nose and malar regions.

Paraneoplastic Pemphigus

Paraneoplastic pemphigus is a disease associated with the presence of benign or malignant neoplasms [11]. The most commonly associated neoplasms include non-Hodgkin's lymphoma and chronic lymphocytic leukemia, which account for around 67% of all the paraneoplastic pemphigus cases. Castleman's disease is associated with about 10% of the paraneoplastic pemphigus cases. This disease is not associated with common tumors, such as breast or colon carcinomas.

The structure of the blisters can range from being flaccid and fragile, like in pemphigus vulgaris, to being stronger more tense blisters, such as the one seen in bullous pemphigoid [11]. Erosions can also be more vegetative in nature. However, a key clinical feature that can be used to distinguish from pemphigus vulgaris is the presence of the reddened lesions and vesicles on the patient's palms and soles, which is a very rare observation in pemphigus vulgaris patients [11].

At the onset of the disease, the most common clinical sign of paraneoplastic pemphigus is intractable stomatitis, in which erosions and ulcerations are found on the oropharynx up to the vermillion lip [11]. This disease also commonly causes pseudomembranous conjunctivitis, which may become more and more severe until it destroys the conjunctival fornices. There are also erosions commonly seen in the genital mucosal areas, as well as the nasopharyngeal areas [11].

Herpetiform Pemphigus

This is seen as a clinical variant of pemphigus foliaceus in most cases and can also be a clinical variant of pemphigus vulgaris [12]. The clinical presentation of herpetiform pemphigus is milder than the presentation in both pemphigus foliaceus and involves red itchy erosions and blisters in a herpetiform pattern. It also involves subcorneal pustules and eosinophilic spongiosis [12]. Unlike PV and PF, no acantholysis is seen histologically. Depending on which clinical variant it is, the disease will involve IgG antibodies to desmoglein 1 or 3 and will have a milder clinical presentation of pemphigus foliaceus or pemphigus vulgaris, respectively [12].

Drug-Induced Pemphigus

Patients may produce antibodies to desmoglein proteins in response to some drugs, or these drugs may affect the function of the desmoglein proteins to induce pemphigus [1]. These drugs include penicillamine and captopril. Penicillamine is usually used in rheumatoid arthritis treatment and in Wilson's disease, or to treat cystinuria, and can cause pemphigus foliaceus or pemphigus vulgaris [1]. However, it is four times more likely to cause pemphigus foliaceus than pemphigus vulgaris. Captopril is an angiotensin-converting enzyme (ACE) inhibitor, which also can cause pemphigus. Usually when the patient is taken off the drug, the pemphigus goes into remission, but this is not always the case [1].

Immunoglobulin A Pemphigus

Unlike all other types of pemphigus, immunoglobulin A (IgA) pemphigus involves IgA autoantibodies against antigens on the cell surface of keratinocytes [13]. This disease is classified into two subtypes: subcorneal pustular dermatosis (SPD) and intraepidermal neutrophilic (IEN) type. In the SPD type, patients have an annular pattern of red pustules with crusting found in the center of the ring pattern of pustules [13]. In the IEN type, the arrangement of the red pustules resembles a sunflower. The pustules and lesions are often pruritic and are most commonly found in the axilla and groin areas. These lesions can also be found on the trunk, on the lower abdomen, and on the proximal parts of arms and legs [13].

Pemphigoid Group of Diseases

The pemphigoid group of diseases includes two major diseases: bullous pemphigoid and cicatricial pemphigoid. Pemphigoid diseases involve subepidermal autoantibodies against proteins in the basement membrane associated with the epidermis.

Bullous Pemphigoid

Bullous pemphigoid is the most common type of disease involving antibodies targeting subepidermal antigens [4]. This is also a chronic blistering disease like pemphigus vulgaris; however, it mainly affects people over the age of 60, and the blisters mainly cover the arms and legs, as well as the trunk area of the patients [4, 14]. In this condition, the blisters are itchy, unlike the ones in pemphigus foliaceus, and they are rarely found in the mucous membranes of the mouth [14]. It has spontaneous exacerbations and remissions and has a high rate of morbidity. It involves pruritic lesions that affect the skin in large generalized areas, and it affects the whole body; however, in its early stages in rare variants of the disease, it can be misdiagnosed because the lesions are more eczematous and may be more localized [4]. The antigens targeted by the autoantibodies in this disease are parts of hemidesmosomes, which are the junctional complexes found between the epidermis and basement membrane. This disease has two distinct phases: the non-bullous phase and the bullous phase. In the non-bullous phase, this disease is quite non-specific and involves mild to severe intractable pruritic skin [4]. There may also be eczematous or urticarial lesion involvement, and this ranges from weeks to months. Then in the bullous phase, tense, clear fluid-filled blisters take up an annular arrangement on the abdomen, limbs, and lower trunk. These lesions are between 1 and 4 cm in diameter [4].

Cicatricial Pemphigoid

Cicatricial pemphigoid, unlike bullous pemphigoid, mainly affects the mucous membranes [1]. It most commonly affects the oral and conjunctival mucosae and is a chronic disease that can cause long-term complications due to scarring. Histological and immunofluorescence studies can help to distinguish this from pemphigus vulgaris, which also mainly affects oral mucosa.

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